



E-PAK® SiliaMetS® SiliaCarb™



## Screening and Efficient Removal of Ruthenium 3<sup>rd</sup> Generation Grubbs Catalyst

With the increasing use of metathesis in the pharmaceutical industry, the removal of the metal catalyst has become a focus. One of the most popular metals as a catalyst is ruthenium, due to being air stable, highly active and versatile for all types of metathesis. To investigate the efficiency of the SiliaCarb activated carbons and SiliaMetS metal scavengers at removing ruthenium, a ring-closing metathesis was performed using the 3<sup>rd</sup> generation Grubbs catalysts on a functionalized diene. This Application Note details the screening of the bulk SiliaCarb and SiliaMetS as well as the experimental conditions to be transferred to E-PAK.

---

**LEARN MORE**about E-PAK in our brochure "*Solutions for Scavenging of Metal & Organic Impurities (BROSCA)*".



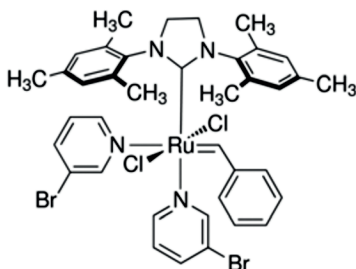
# Screening and Efficient Removal of Ruthenium 3<sup>rd</sup> Generation Grubbs Catalyst

## INTRODUCTION

Since its first report in the 1950s by chemists at Dupont,<sup>1</sup> the metathesis reaction has become increasingly popular due to its broad applications from the synthesis of pesticides to complex natural products.<sup>2</sup> In fact, the 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock, three scientists who further developed this reaction and its catalysts, making metathesis reactions more widely applicable in industry.<sup>3</sup> Named after one of the Nobel laureates, the ruthenium-based Grubbs catalyst is the most popular for such reactions due to being air-stable, highly active, and versatile. One of the most interesting iterations of this catalyst was developed by Love et al. in 2002. Better known as the 3<sup>rd</sup> generation Grubbs catalyst, where the triphenylphosphine ligands are replaced by 3-bromo-pyridines giving a more active catalyst able to react with a wider range of substrates in various metathesis transformations.<sup>4</sup>

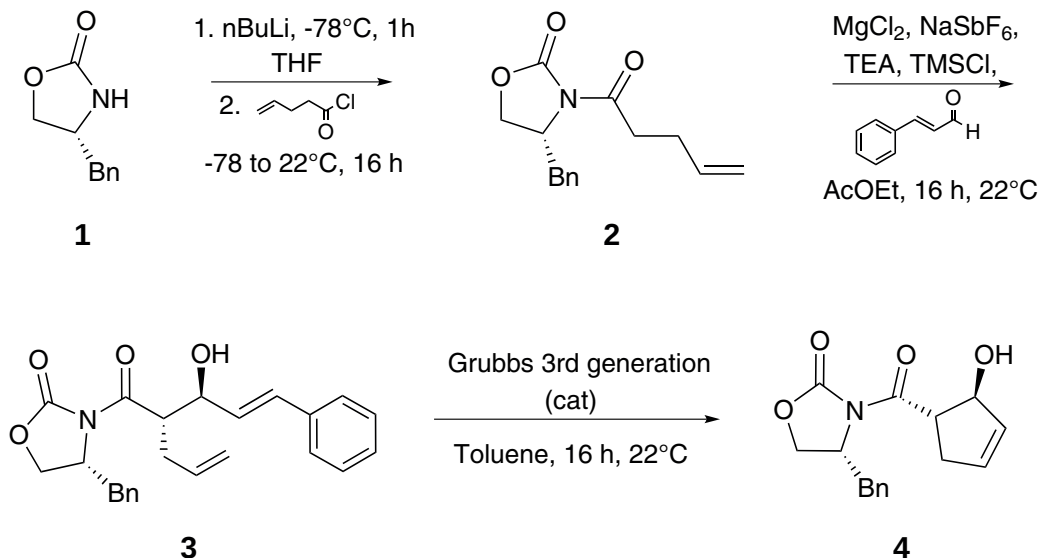
This Application Note details the scavenging efficiency of the SiliaCarb activated carbons and SiliaMetS metal scavengers to remove ruthenium, in both bulk and E-PAK cartridge mode. A ring-closing metathesis using the 3<sup>rd</sup> generation Grubbs catalyst was performed on diene **3** to obtain the cyclopentenol **4** (Figure 1).

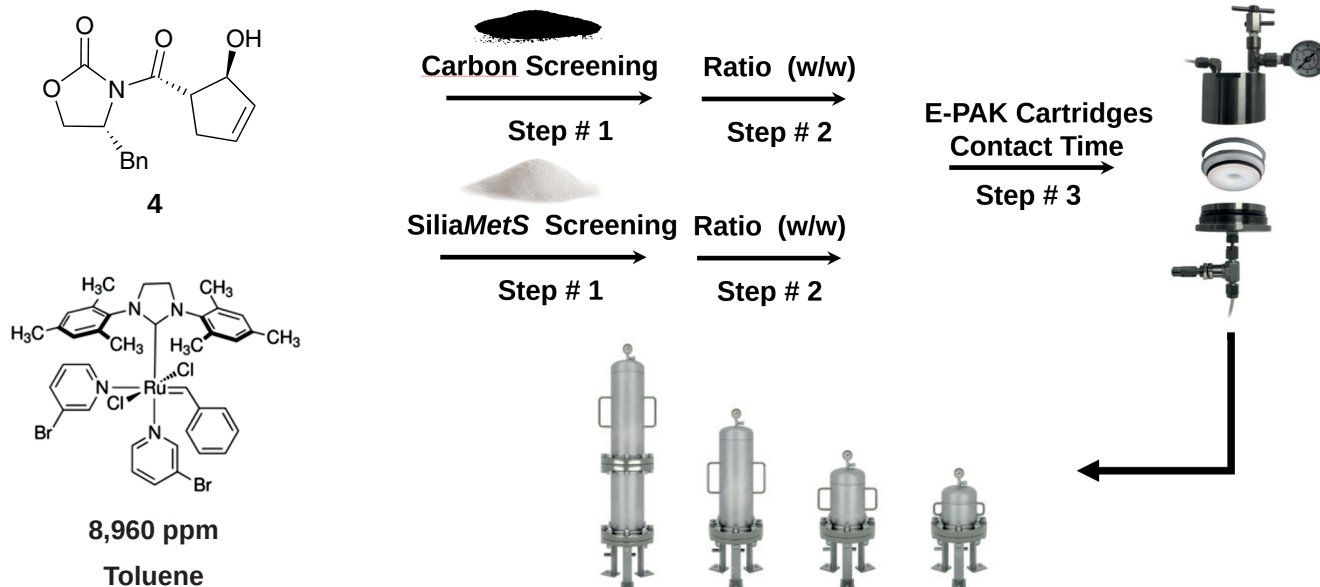
Figure 1: 3<sup>rd</sup> generation Grubbs catalyst



The following reaction was inspired from a sequence reported by Peat *et al.*,<sup>5</sup> in the synthesis of an improved antiviral molecule (used as a hepatitis C replication inhibitor). The ring-closing metathesis step of the reaction involving the 3<sup>rd</sup> generation Grubbs catalyst yielded 15.5 g of crude product **4** contaminated with 8,960 mg/kg of residual ruthenium.

Figure 2: Synthesis of an improved antiviral molecule involving the 3<sup>rd</sup> generation Grubbs catalyst





## STEP 1: SILIACARB ACTIVATED CARBON SCREENING IN BULK

A preliminary screening was performed with SiliaCarb activated carbons to remove as much ruthenium residue as possible from the crude mixture of product **4**. The goal of this screening was to find the best SiliaCarb as well as the optimal conditions to yield the highest scavenging.

### General method

A quantity of 20 mg (100 % w/w) of each SiliaCarb activated carbon was first pre-weighed in polypropylene tubes. Volumes of 4 mL of API solution (0.5 g in 100 mL of ethyl acetate) were then added into the four tubes and mixed for 1 hour at room temperature (22°C), followed by the collection and filtration (0.45  $\mu\text{m}$ ) of 0.5 mL of each solution. This last step was repeated after the 4-hour mark.

A second screening following the same procedure was repeated at 50°C, again with sample collection at 1 and 4 hours.

Samples were analyzed by ICP-OES for ruthenium content. The scavenging results were reported in Table 1.


**Table 1:** Ruthenium scavenging yields (%) of various SiliaCarb (100 % w/w) at 22°C and 50°C in ethyl acetate

Ruthenium Scavenging Yields (%) of Various SiliaCarb (100 % w/w) at 22°C and 50°C in Ethyl Acetate				
Activated Carbon	22°C		50°C	
	1 h	4 h	1 h	4 h
SiliaCarb CA	60	60	67	72
SiliaCarb HA	55	57	58	62
SiliaCarb VA	36	38	38	41
SiliaCarb VW	60	62	64	68

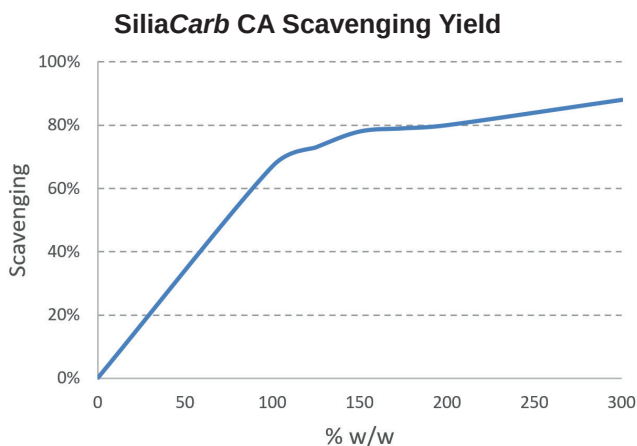


Slight scavenging yield improvements were observed for all activated carbons when both time and temperature were increased (*Table 1*). Out of the four carbons screened, SiliaCarb CA provided the highest yield at 72 % (4 hours, 55°C) and therefore was selected for further optimizations tests. The first parameter to be optimized was loading percentage (*Table 2 and Figure 3*).

**Table 2:** Ruthenium scavenging yields (%) of SiliaCarb CA for different loading at 50°C in ethyl acetate, for 1 h

 <b>Ruthenium Scavenging Yields (%) of SiliaCarb CA for Different Loading at 50°C in Ethyl Acetate, for 1 h</b>	
% (w/w)	SiliaCarb CA
100 %	67
125 %	73
150 %	78
175 %	79
200 %	80
300 %	88


**Figure 3:** SiliaCarb CA scavenging yield



From the results obtained, 125 % w/w SiliaCarb to API ratio was selected as only marginal scavenging yield was observed with higher loadings.

The next parameter that was optimized after loading, was solvent selection. From previous R&D experiments, solvent selection has been known to dramatically affect the adsorption yield when using activated carbon. Therefore, SiliaCarb CA was tested at 50°C in several solvents using 125 % w/w for 1 hour (*Table 3*).

**Table 3:** Ruthenium scavenging yields (%) of SiliaCarb CA (125 % w/w) in various solvents at 50°C, for 1 h

 <b>Ruthenium Scavenging Yields (%) of SiliaCarb CA (125 % w/w) in Various Solvents at 50°C, for 1 h</b>	
Solvent	SiliaCarb CA
Acetone	60
Ethyl Acetate	73
Methanol	81
THF	39
Toluene	67



Methanol gave the best scavenging yields with up to 81 % when keeping reaction time, loading and temperature constant.

These screening experiments determined the following set of conditions to be the best for the scavenging of ruthenium:

- SiliaCarb CA activated carbon for scavenging
- Loading of 125 % w/w
- Reaction temperature of 50°C
- Reaction time of at least 1 hour
- Methanol as a solvent

Using this set of conditions, ruthenium contamination was reduced from 8,960 mg/kg to 1,702 mg/kg.

## STEP 2: SILIAMETS METAL SCAVENGERS SCREENING IN BULK

Following the screening of SiliaCarb to get the most efficient purification conditions, a similar exercise was done with SiliaMetS to further remove ruthenium from solution.

### General method

A 1.25 g portion of pre-treated (*with SiliaCarb CA*) crude contaminated with ruthenium was dissolved in 100 mL of methanol.

Quantities of 25 mg (*at 50 % w/w*) for 12 different SiliaMetS metal scavengers were pre-weighed in polypropylene tubes. Then, 4 mL of the dissolved pre-treated crude solution was added into each tube followed by mixing for 1 and 4 hours at room temperature (22°C). Afterward, 0.5 mL of each solution was collected and filtered (0.45  $\mu\text{m}$ ), providing 12 samples per time point to be analyzed by ICP-OES for ruthenium content. The same experiment was repeated at 50°C (*Table 4*).

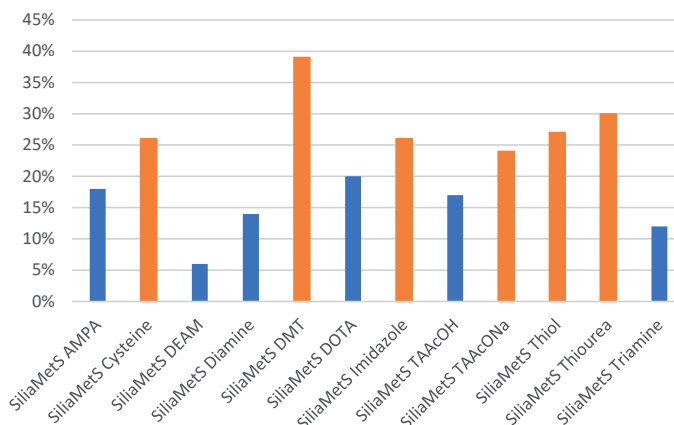
**Table 4:** Ruthenium scavenging yields (%) using SiliaMetS (50 % w/w) at 22°C and 50°C in methanol

Metal Scavengers	Ruthenium Scavenging Yields (%) Using SiliaMetS (50 % w/w) at 22°C and 50°C in Methanol			
	22°C		50°C	
	1 h	4 h	1 h	4 h
SiliaMetS AMPA	0	12	15	18
SiliaMetS Cysteine	5	18	8	26
SiliaMetS DEAM	4	6	6	6
SiliaMetS Diamine	6	11	8	14
SiliaMetS DMT	28	35	31	39
SiliaMetS DOTA	0	12	0	20
SiliaMetS Imidazole	17	21	22	26
SiliaMetS TAAcOH	4	16	15	17
SiliaMetS TAAcONa	12	18	16	24
SiliaMetS Thiol	20	22	22	27
SiliaMetS Thiourea	11	24	22	30
SiliaMetS Triamine	10	10	10	12



Figure 4: Ruthenium scavenging yields of various SiliaMetS at 50°C for 4 hours

## Ruthenium Scavenging Yields of Various SiliaMetS at 50°C for 4 Hours



Exceptionally low yields were obtained at room temperature, while modest scavenging yields up to 39 %, were obtained at 50°C for 4 hours. Higher temperature and longer contact time had a positive effect for most of the scavengers. Further tests for optimization at 50°C were performed with an increased loading ratio using the top six SiliaMetS (Figure 4 orange bars) from the first part of the screening (Table 5).

Table 5: Ruthenium scavenging yields (%) for top performing SiliaMetS at different loading at 50°C in methanol

Ruthenium Scavenging Yields (%) for Top Performing SiliaMetS at Different Loading at 50°C in Methanol						
Metal Scavengers	100 % w/w		150 % w/w		200 % w/w	
	1 h	4 h	1 h	4 h	1 h	4 h
SiliaMetS Cysteine	14	25	16	27	19	27
SiliaMetS DMT	36	55	36	57	36	58
SiliaMetS Imidazole	32	34	32	35	32	35
SiliaMetS TAAcONa	15	39	17	41	20	42
SiliaMetS Thiol	24	48	26	52	26	52
SiliaMetS Thiourea	30	31	32	35	33	36

Out of the six top-performing scavengers from the initial screening, DMT, Thiol and TAAcONa were the most promising scavengers with yields up to 58 % when optimizing for loading ratio. For these three SiliaMetS, considering the very slight improvement with increased loading, 100 % w/w ratio was taken for the rest of the study. Having the loading ratio selected, contact time optimization was the next step. Consequently, several tests were performed for 24 hours with 100 % w/w in methanol (Table 6).


Table 6: Ruthenium scavenging yields (%) for various SiliaMetS at 4 and 24 h in methanol at 50°C

Ruthenium Scavenging Yields (%) for Various SiliaMetS at 4 and 24 h in Methanol at 50°C				
Metal Scavengers	100 % w/w		150 % w/w	
	4 h	24 h	4 h	24 h
SiliaMetS DMT	55	57	57	72
SiliaMetS TAAcONa	39	59	41	60
SiliaMetS Thiol	48	66	52	71



The extended contact time had a positive effect on the scavenging yields with up to 72 % removal at 24 hours. In certain cases, combining scavengers can lead to increased yields and knowing that ruthenium can have different oxidation states during the catalytic cycle, it was worth trying. Therefore, combinations of the above three scavengers at 100 % and 150 % w/w ratio were tested (Table 7).


**Table 7:** Ruthenium scavenging yields (%) using a combination of SiliaMetS at 50°C in methanol

 <b>Ruthenium Scavenging Yields (%) Using a Combination of SiliaMetS at 50°C in Methanol</b>			
Metal Scavengers Combination	Ratio (%)	4 h	24 h
SiliaMetS DMT	100	48	70
SiliaMetS TAAcONa	100		
SiliaMetS DMT	150	49	72
SiliaMetS TAAcONa	100		
SiliaMetS DMT	100	52	66
SiliaMetS Thiol	100		
SiliaMetS DMT	150	55	71
SiliaMetS Thiol	150		
SiliaMetS TAAcONa	100	54	73
SiliaMetS Thiol	100		
SiliaMetS TAAcONa	100	52	71
SiliaMetS Thiol	150		

In this case, no significant improvement was observed for the various combinations of SiliaMetS. Hence for the final parameter optimization tests, DMT and Thiol, the two most popular scavengers in SiliCycle's portfolio, were chosen as they had better individual results compared to TAAcONa.

To confirm that methanol was indeed still the best solvent, a screening was conducted. In this case, however, solvents with higher boiling points than methanol ( $\geq 65^\circ\text{C}$ ) were chosen to see if by increasing temperature, yields would greatly improve. Since the dried crude 4 (previously treated with SiliaCarb CA) wasn't soluble in isopropanol, acetonitrile, 2-methyltetrahydrofuran or ethyl acetate, only toluene and DMF were included in this study (Table 8).

**Table 8:** Ruthenium scavenging yields (%) using SiliaMetS DMT and Thiol at various temperatures for 4 and 24 h

 <b>Ruthenium Scavenging Yields (%) Using SiliaMetS DMT and Thiol at Various Temperatures for 4 and 24 h</b>				
Metal Scavengers	Solvent	Temperature (°C)	4 h	24 h
SiliaMetS DMT	Methanol	50	55	68
SiliaMetS Thiol			48	66
SiliaMetS DMT	DMF	65	16	43
SiliaMetS Thiol			23	46
SiliaMetS DMT	Toluene	65	76	95
SiliaMetS Thiol			73	95

Surprisingly, significant improvements were observed in toluene at 65°C with yields up to 95 % for both scavengers. From the results in Table 8, toluene gave similarly high yields with both scavengers and outperformed methanol. It should be noted that DMF underperformed compared to methanol underlining that while temperature is important, solvent selection is equally so.



The screening experiments determined the following set of conditions to be the best for the scavenging of ruthenium with SiliaMetS:

- Loading of 100 % w/w of either SiliaMetS Thiol or DMT
- Reaction temperature of 65°C
- Reaction time of 24 hours
- Toluene as a solvent


### STEP 3: E-PAK EXPERIMENTS

Once the most efficient conditions were determined for both SiliaCarb and SiliaMetS, the parameters were transferred to the E-PAK set-up following the same two step purification procedure.

#### E-PAK SiliaCarb CA treatment

A 5 x 1 cm E-PAK SiliaCarb CA (containing 4.4 g of activated carbon) was inserted in the appropriate housing with 150 mL of methanol used to pre-condition the unit and then discarded. A solution heated at 50°C, with 3.6 g of crude **4** dissolved in 150 mL of methanol was recirculated for 3 hours through the cartridge (125 % w/w, 25 mL/min flow rate). No back pressure was measured. After the 3-hour run, the whole system was flushed with 100 mL of clean methanol, providing about 250 mL of the treated mixture. Following solvent evaporation, 2.7 g of treated compound **4** was recovered (76 % recovery) with 845 mg/kg of residual ruthenium (Table 9).

**Table 9:** Ruthenium scavenging yields of E-PAK SiliaCarb CA (125 % w/w) treatment of crude **4** in methanol

 Ruthenium Scavenging Yields of E-PAK SiliaCarb CA (125 % w/w) Treatment of Crude <b>4</b> in Methanol		
Time (h)	[Ru] (mg/kg)	Yield (%)
0	8,960	---
1	1030	88
2	880	90
3	845	91

#### E-PAK SiliaMetS DMT treatment

A 5 x 1 cm E-PAK SiliaMetS DMT cartridge (containing 8 g of grafted DMT silica-100 % w/w) was inserted in the appropriate housing with 150 mL of toluene used to pre-condition the unit. The solvent was discarded.

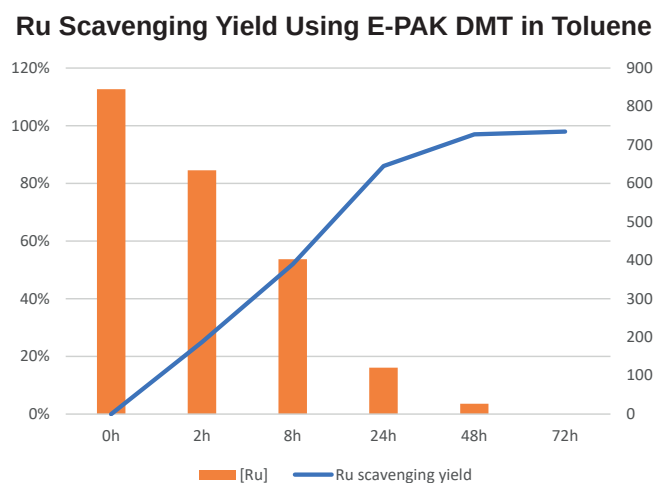
A solution containing 8 g of pre-treated product **4** in 250 mL of toluene was heated at 65°C and recirculated for 72 hours, through the cartridge (20 mL/min flow). No back pressure was measured. Samples of 0.5 mL were collected after the following time points: 2, 8, 24, 48 and 72 hours. Samples from each time point were analyzed by ICP-OES for ruthenium content.

The whole cartridge was flushed with 100 mL of clean toluene, and the solvent was evaporated, providing 7.5 g of product **4** (recovery of 94 %) with 17 mg/kg (98 % scavenging) of residual ruthenium (Table 10).



**Table 10:** Ruthenium scavenging yields with E-PAK SiliaMetS DMT (100 % w/w) treatment at 65°C in toluene

Ruthenium Scavenging Yields with E-PAK SiliaMetS DMT (100 % w/w) Treatment at 65°C in Toluene		
Time (h)	[Ru] (mg/kg)	Yield (%)
Start	845	---
2 h	634	25
8 h	403	52
24 h	121	86
48 h	27	97
72 h	17	98

**Figure 5:** Ruthenium scavenging yield using E-PAK DMT at 65°C in toluene

The two step E-PAK method decreased ruthenium residue concentration from 8,960 mg/kg to 27 mg/kg over 48 hours, and down further to 17 mg/kg over 72 hours which is a 99.8 % scavenging yield.

## CONCLUSIONS

A ring closing metathesis reaction was performed using the 3<sup>rd</sup> generation Grubbs catalyst yielding up to 8,960 mg/kg of residual ruthenium in the crude solution. A screening of both SiliaCarb activated carbons and SiliaMetS metal scavengers was undertaken to establish the best conditions for the removal of ruthenium before transferring to the E-PAK system.

A preliminary treatment with E-PAK SiliaCarb CA removed up to 91 % of ruthenium with 76 % recovery of the final product. It was then followed by the recirculation through the E-PAK SiliaMetS DMT cartridge to further reduce the remaining ruthenium, by > 97 % after 48 hours (94 % recovery).

The entire E-PAK process decreased ruthenium levels from 8,960 to 17 mg/kg, (99.8 % scavenging yield) after 72 hours. The overall yield of product **4** for the combined steps was 71 %.

## References

- <sup>1</sup> Ger. Pat. 1 072 811 **1960**; H.S. Eleuterio, *Chem. Abstr.*, **1961**, 55, 16005
- <sup>2</sup> Handbook of Metathesis; R.H. Grubbs, Ed., Wiley-VCH: New York, **2003**
- <sup>3</sup> Mol, J. C. *J. Mol. Catal. A* **2004**, 213, 39. Hughes, D. et al. *Org. Process Res. Dev.* **2017**, 21, 1938.
- <sup>4</sup> Love, J. A. et al. *Angew. Chem. Int. Ed.* **2002**, 41, 4035.
- <sup>5</sup> Miller, J. F. et al. *J. Med. Chem.* **2014**, 57, 2107.

**DISCOVER OUR BROCHURES**

**METAL & ORGANIC SCAVENGING**

**SiliaMetS<sup>®</sup>** – Metal Scavengers  
**SiliaBond<sup>®</sup>** – Organic Scavengers  
**E-PAK<sup>®</sup>** – Fixed Bed Flow-Through Purification Cartridges



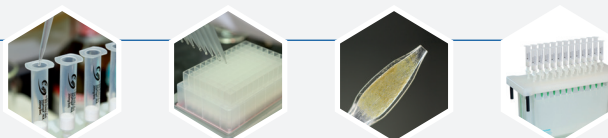
**CHROMATOGRAPHY & PURIFICATION**

**SiliaFlash<sup>®</sup>** – Irregular Silica Gels  
**SiliaSphere<sup>™</sup> PC** – Spherical Silica Gels  
**SiliaBond<sup>®</sup>** – Chromatographic Phases  
**SiliaSep<sup>™</sup>** – Flash Cartridges  
**SiliaPlate<sup>™</sup>** – TLC Plates



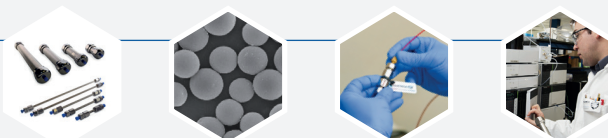
**SAMPLE PREPARATION**

**SiliaPrep<sup>™</sup>** – Silica-based SPE Cartridges & Well Plates  
**SiliaPrepX<sup>™</sup>** – Polymeric SPE Cartridges & Well Plates  
**SiliaPrep<sup>™</sup>** – Micro-SPE Tips



**ANALYTICAL & PREPARATIVE CHROMATOGRAPHY**

**SiliaSphere<sup>™</sup>** – Spherical Silica Gels  
**SiliaChrom<sup>®</sup>** – HPLC Columns



**ORGANIC SYNTHESIS**

**SiliaBond<sup>®</sup>** – Reagents & Oxidants



**R&D SERVICES**

Metal & Organic Scavenging Screening  
 Organic Synthesis  
 Extraction & Purification  
 Custom Column Packing  
 Material Science



**Overseas Offices**